#17
6-7-03

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Maryvonne CHARIOT *et al*

Serial No. 09/605,054 Group Art Unit: 1617

Filed: June 28, 2000 Examiner: Alysia Berman

For: SLOW-RELEASE PHARMACEUTICAL FORMULATIONS CONTAINING MIZOLASTINE

AMENDMENT UNDER RULE 111

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Responsive to the Official Action (Paper No. 15) of December 4, 2002, favorable reconsideration is respectfully requested. In view of the arguments set forth in the prior record in connection with applied art, which are repeated herein by reference, and the following comments.

Applicants note that reliance is placed upon an abstract when the underlying publication is available. If any further reliance is placed on the Desager publication, it should be placed on the underlying document itself, rather than the abstract. [See *Ex parte Jones*, 62 U.S.P.Q.2d 1206, 1208, 1209 (B.P.A.I. 2001).]

The rejection of claims 21, 22, 24 to 26, 30 to 34, 38 and 39 "under 35 U.S.C. §103(a) as being unpatentable over US 4,590,062 ('062) in combination with the HCAPLUS abstract of Desager et al" is respectfully traversed. Desager considers common pharmacokinetics of ten second generation H$_1$-receptor antagonists, with no particular direction to mizolastine, which is only one member of the considered class. Jang ('062) is generically directed to dry compressed compositions for controlled release dosage forms for, *inter alia*, analgesic drugs, anorexic drugs, anthelmintic drugs, anti-asthma drugs, antibacterial drugs, antibiotic and antimicrobial drugs, antiseptic drugs, anticoagulant drugs, anticonvulsent drugs, anti-depressant drugs, anti-diabetic drugs, anti-gout drugs, anti-fungal drugs,

antihistamine drugs, anti-inflammatory drugs, antimalarial drugs, antimigraine drugs, anti-motion-sickness drugs, anti-nausient drugs, antineoplastic drugs, cough and cold preparation drugs, decongestant drugs, diaretic drugs, hormone drugs, muscle relaxant drugs, parasympatholytic drugs, sedative drugs, tranquillizer drugs, agrichemicals, algicides, anti fowling agents, fungicides, insecticides, molescicides, plant growth regulators, rodenticides, fertilizers, flavors, fragrances and perfumes. Among the hundreds of active components actually mentioned by Jang mizolastine does not even appear.

With all due respect, there is absolutely no rationale that would lead anyone of ordinary skill in the art to select mizolastine from Desager and antihistamines from Jang. In the absence of Applicants' disclosure, the art itself would not lead to the combination of these two references for any particular purpose.

Claim 21 calls for a coated sustained release tablet consisting essentially of from 0.5% to 12% by weight of mizolastine, a fatty matrix, an organic acid and a coating. Nothing is found in either reference that would lead to all of the express details of this claim. Claim 22 further limits claim 21 to a tablet having a dissolution profile which is pH independent; nothing is found in either reference which leads to this express property.

Claim 24 is directed to a dosage form which comprises a coated tablet having a sustained-release core; no suggestion or disclosure of the details of this claim is found in either reference.

Claim 25 further limits claim 24 to a dosage form with a specific weight ratio of mizolastine to the organic acid, which ratio is neither disclosed nor suggested by either reference.

Claim 26 further limits claim 24 to one wherein the fatty matrix is further limited.

Claim 30 further limits claim 24 to a dosage form containing from 1 to 25 mg of mizolastine.

Claim 31 is directed to a tablet having a dissolution profile which is pH independent, and in vivo mizolastine release which prevents any plasma peak, a mizolastine bioavailability which is not decreased relative to that of an immediate release formulation, and wherein the mizolastine comprises a defined percentage weight of the tablet; this combination of properties is neither disclosed nor suggested by either reference.

Claim 32 further limits claim 31 to a tablet which has a specified dissolution profile that is

neither disclosed nor suggested by either reference. Please note in this regard that Jang, Table I, illustrates only 56% of ascorbic acid released after five hours, whereas claim 32 calls for 100% of mizolastine dissolved in from three to five hours. No relevant teaching is found in the applied art.

Claim 33 further limits the tablet of claim 31 to a specified weight ratio between mizolastine and the organic acid; such ratio is neither disclosed nor suggested by the applied art.

Claim 34 further limits claim 31 with regard to the fatty matrix.

Claim 38 further limits the tablet of claim 31 to the content of mizolastine.

Claim 39 expressly limits the organic acid to one which has a pK of two or more.

Although Jang is directed to compositions for control release dosage forms, his exemplified control release provides a 56% release in five hours (Table I) and 100% release in from 10.5 to 31.6 hours (Table V). Jang is not concerned with specific drugs and their needs.

Jang is nothing more than an invitation to experiment with regard to vastly different groups of drugs and fails to provide examples illustrative of each of the groups, much less of antihistamines, particularly of the type to which mizolastine belongs. The actual formulations required for the diverse groups mentioned by Jang would vary considerably, and no direction whatsoever is provided with regard to mizolastine. Each of the references relied upon provides nothing more than an invitation to experiment.

Actually, Desager is only one of the numerous publications directed to antihistamines, and discloses information about the second generation of antihistamines, such as mizolastine, known to be free of drowsiness. However, it gives no information concerning a formulation for use, and, consequently, no predictable information concerning the effect of pH on dissolution profile or possible pharmaceutical forms including it.

The pH independence is one of the major aims of the present invention (among other claim properties, such as preventing any plasma peak and preventing mizolastine bioavailability decrease).

Any disclosure in Jang relating to varying a formula is merely an invitation to experiment, rather than a teaching of that called for by any of Applicants' claims.

Issue is respectfully taken with the allegation: "one of ordinary skill in the art would expect a composition containing the same components to exhibit the same properties". This is tantamount to

saying that a drink with 99% scotch and 1% water would have the same properties as a drink with 99% water and 1% scotch because they have the same components.

Issue is respectfully taken with regard to the burden being shifted to Applicants, particularly in view of the fact that no detailed compositions with antihistamines are shown by any of the applied art, thus making it impossible to compare that which is called for by Applicants' claims with any disclosure in the prior art relied upon It is only considered within the skill of the art to adjust parameters when the parameters are known to be result dependent, and there is nothing in the applied art that even remotely suggests previously noted properties of Applicants' claim compositions.

With regard to functional language, there is a clear difference between what is commonly perceived as such and the identification of properties. The reference to the *Eli Lilly* Case, is submitted to be inappropriate. The highly undeveloped art with regard to genetic engineering has been treated differently from other arts with regard to functional language. The only portion of Title 35 U.S.C. that makes any reference to the use of statements of function specifically authorizes such use. All elements of a combination can be claimed in terms of what they do as well as in terms of what they are. *In re Fuetterer*, 138 US.P.Q. 217, 221 (CCPA 1963).

There is nothing in the applied art that would even remotely suggest that Applicants' claimed tablets would be pH independent, would permit 100% release of the active component in five hours, would have an in vivo mizolastine release which prevents any plasma peak, or wherein mizolastine bioavailability is not decreased relative to that of an immediate release formulation. There is no reason to believe that one of ordinary skill in the art would find success of those goals apparent or obvious from anything found in the applied art. [See *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).]

The rejection of claims 23, 27 to 29, 35 to 37 and 39 to 43 "under 35 U.S.C. §103(a) as being unpatentable over US 4,590,062 ('062) in combination with Desager et al.... and further in view of US 5,102,666 ('666)" is also respectfully traversed in the same manner and for the same reasons as set forth in the preceding remarks. Acharya ('666) does not in any way overcome the previously noted deficiencies of the other two references.

Acharya is directed to "a polymeric delivery system which is formed through the interaction of a calcium polycarbophil type composition with water and/or other cosolvent" (column 2, lines 64

to 67). There is no reason that anyone of ordinary skill in the art would consult this reference in dealing with the problems faced and solved by Applicants' claimed invention.

Moreover, Acharya is generically concerned with in excess of 30 different classes of drugs, only one of which concerns antihistamines. In addition, mizolastine is not among the antihistamines identified by this reference.

Tartaric acid is referred to in the following context:

> Other ingredients that can be present in the compositions of the present invention include breath fresheners and flavors, e.g., spearmint oil, peppermint oil, cinamaldehyde, cetyl pyridinium chloride, menthol saccharine sodium, glycyrrhizin, malt syrup, citric acid, tartaric acid, lemon oil, citrus flavor, and the like, sodium fluoride and the like, anti-plaque/anti-bacterial compositions suitable to treat or prevent periodontal disease, e.g., chlorbutanol, chlorothymol, chlorohexidine, their salts, and the like, dental pain control ingredients, e.g. benzocaine, lidocaine and the like.

There would be no direction or suggestion of selecting antihistamines from the huge variety of medicinal agents or for selecting tartaric acid from the diverse "breath fresheners and flavors" from a reference directed to "a polymeric delivery system which is formed through the interaction of a calcium polycarbophil type composition with water and/or other cosolvent." This is not the system which is the subject of Applicants' claims. The application of Acharya is clearly and unequivocally an example of retrospective reconstruction based solely on Applicants' disclosure.

With regard to claim 29, please note that it specifies a particular ratio between the mizolastine and the L-tartaric acid, which is neither disclosed nor suggested by Acharya. This also applies to claims 37 and 40 to 43.

Claim 43 further calls for a tablet having a dissolution profile which is independent of pH and is one in which about 50% of the mizolastine is dissolved in one hour and 100% of the mizolastine is dissolved in 3 to 5 hours. None of this is even remotely suggested by any applied art.

Please note that the reference to tartaric acid by Acharya is clearly and solely optional. There is absolutely no reason to believe from Acharya that addition of tartaric acid could improve the efficacy of a pharmaceutical formulation, as provided by Applicants' claimed invention. In Applicants' claimed subject matter tartaric acid improves the provided sustained release formulation as shown in Figures 1 and 2 of Applicants' parent application (USP 6,165,507). This is clearly an unpredictable and unobvious effect.

Of further import is the fact that Acharya's polycarbophil type composition has a complex hydrogel matrix structure (column 4, lines 27 to 38) which is significantly different from Applicants' fatty matrix. The hydrogel matrix is intended to give a release of a very extended and indefinite period up to several months (column 5, lines 40 to 42), contrary to Applicants' release of 100% mizolastine in from 3 to 5 hours.

Any allegations of what would have been obvious to one of ordinary skill in the art are respectfully challenged in the absence of clear support in the applied art itself. No such support is provided in Paper No. 15.

In the rationale presented by Paper No. 15 it appears that there may be some confusion between functionality at the point of novelty and a recitation of properties; there is a clear distinction between the two.

In order to clarify the evidence relied upon with regard to the effect of tartaric acid, Applicants submit herewith a copy of USP 6,165,507, previously referred to.

Having overcome all outstanding grounds of rejection, favorable action on the merits is in order and is respectfully solicited.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By Stuart Rosenberg RN 19007
for Harvey B. Jacobson, Jr.
Registration No. 20,851

Date: May 30, 2003
(202) 638-6666
400 Seventh Street, N.W.
Washington, D.C. 20004
IMA/ccm
Atty. Dkt. No.: P62285US1